REMARKS

Claims 12-20 are pending. Claims 1-11 have been canceled as non-elected, without prejudice to, or disclaimer of, the subject matter therein. Claim 16 has been amended to correct an obvious typographical error.

Additionally, Applicants wish to note that commonly owned, copending Application No. 10/441,947, claiming common priority to the parent provisional Application No. 60/112,534, is currently assigned to Examiner Dwayne Jones in Art Unit 1614. The immediate parent of the pending application, Application No. 09/882,935, is now issued as U.S. Patent No. 6,734,215.

Rejections under 35 U.S.C. §103(a) are Traversed

Crooks, in view of The Merck Manual

Claims 12-20 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,691,365 to Crooks, *et al.* (Crooks), in view of The Merck Manual. The Examiner stated that:

> Crooks et al. teach nicotine analogs that have nicotinic receptor *antagonist* properties, that are useful in treatment of cognitive disorders such as Parkinson's disease (see abstract). It does not teach treatment of Tourette Syndrome; however, it would have been obvious to employ a nicotine receptor antagonist such as mecamylamine to treat symptoms of Tourette Syndrome motivated by the teaching of Crooks et al. who teaches treatment of Neurologic disorders such as Parkinson's disease with nicotine receptor *antagonists* and the Merck Manual that teaches that dyskinesia's such as Tourette Syndrome are due to basal ganglia disorders (a neurologic disorder).
>
> The patent does not teach treatment with the R isomer that is substantially free of the S isomer. It would have been obvious to employ the R isomer that is substantially free of the S isomer. As legal authority in this case the examiner cites *In re Adamson and Duffin* 125 USPQ 233. The case sets forth the requirements of patentability with regard to stereoisomers as follows:
>
> 1) The existence of a racemate is, in and of itself, sufficient to render obvious any individual stereoisomers contained within; no express suggestion of isomer separation is needed. See the first paragraph on page 235.
>
> 2) *One skilled in the art expects that individual stereoisomers will differ significantly in physiological/pharmacological activity and toxicity, because living systems are chiral and thus preferentially process certain stereochemical configurations over others.* See page 234, the third full paragraph and page 235, the fifth full paragraph on the page.

Office Action at pages 4-5 (emphasis added). In view of the following remarks, Applicants respectfully traverse the rejection.

Initially, Applicants note that one aspect of the present invention is the discovery that mecamylamine exhibits a *partial agonist* effect at nicotinic receptors. In providing the benefits of the present invention for treatment of Tourette's Syndrome, bipolar disorder, depression, an anxiety disorder, schizophrenia, a seizure disorder, Parkinson's disease, and attention deficit hyperactivity disorder, exo-R-mecamylamine is acting as a partial agonist. Such effects were unexpected in view of the general characterization of mecamylamine as a nicotine antagonist. Further, as noted below, certain additional, unexpected pharmacological characteristics of the exo-R isomer were discovered as part of the presently disclosed invention.

As noted by the Examiner, Crooks discusses nicotinic receptor *antagonists*. Nicotinic receptor antagonists are not recited in Applicants' claims. Applicants' pending independent claims both recite "a therapeutically effective amount of exo-R-mecamylamine or a pharmaceutically acceptable salt thereof, substantially free of exo-S-mecamylamine." See claims 12 and 16. No teaching by Crooks of particular nicotinic receptor antagonists in combination with the asserted teaching of the Merck Manual could possibly render Applicants' claims unpatentable. No combination of Crooks and the Merck Manual teach or suggest any mecamylamine stereoisomer or any nicotine receptor partial agonist for the treatment of the presently recited disorders.

Further, regarding the Examiner's comment that the "claims must specify 'isolation', 'optical purity', etc or they are read upon by the racemate," Applicants respectfully point out that the phrase "substantially free of exo-S-mecamylamine" is defined in the Definitions section of Applicants' specification as follows: "The term 'substantially free of the exo-S-mecamylamine hydrochloride' as used herein means that the composition contains at least about 90% by weight of exo-R-mecamylamine--and less than about 10% by weight of exo-S-mecamylamine." See the Specification at page 11, lines 5-7. Applicants are not aware of any disclosure of a "racemate" composition encompassed by this definition of the exo-R-mecamylamine as recited in Applicants' claims. Accordingly, it is Applicants' position that no amendment is necessary.

For at least the foregoing reasons, no combination of Crooks and the Merck manual could provide Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

University of South Florida Research Foundation WO 99/07378 A1

Claims 12-20 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over University of South Florida Research Foundation WO 99/07378 Al (USF). The Examiner stated that:

> University of South Florida teaches administration of a nicotine antagonist, particularly mecamylamine (see abstract) and mecamylamine stereoisomers (see claim 8) for neuropsychiatric disorders such as Tourette syndrome, schizophrenia, depression, bipolar disorders, attention deficit hyperactivity disorder, and obsessivecompulsive disorder.
> It does not teach the R stereoisomer. It would have been obvious to employ the R isomer that is substantially free of the S isomer.

Office Action at page 5. The Examiner again cited *In re Adamson and Duffin*, as noted above. In view of the following remarks, Applicants respectfully traverse the rejection.

Initially, Applicants note that all pending claims are fully supported by parent disclosures, at least as early as the filing of the international parent application PCT/US99/30137 (WO 00/35280) on December 16, 1999. Therefore, WO 99/07378 A1, published on February 18, 1999, is not properly cited as prior art against Applicants' claims. Accordingly, the rejection is in error and must be withdrawn.

Regardless of the propriety of the citation, Applicants note that the USF reference fails to teach or suggest any pharmaceutical composition or treatment method using any single isomer of mecamylamine, substantially free of the other isomer. The following remarks to further illustrate the patentability of the present claims over any disclosure of racemate compositions or methods in the USF reference.

In *In re Doyle*, the Federal Circuit made the following observations:

> Altering the relative orientation of the groups bonded to the various chiral centers of a molecule (i.e., creating a different stereoisomer of the compound) can have profound effects on the compound's properties, especially with respect to how the compound interacts with other chiral molecules. These effects are important in pharmaceutical chemistry, among other areas of chemical endeavor,

> because often only one of the stereoisomers of a particular target compound possesses the desired pharmacological activity.

In re Doyle, 63 USPQ2d 1161, 1162 (Fed. Cir. 2002). Further, the passage from *In re Adamson and Duffin* quoted by by the Examiner states that:

> One skilled in the art expects that individual stereoisomers will differ significantly in physiological/pharmacological activity and toxicity, because living systems are chiral and thus preferentially process certain stereochemical configurations over others.

The fact that one of skill in the art would expect "that the individual stereoisomers will differ significantly in physiological/pharmacological activity and toxicity" supports the *nonobviousness* of beneficial pharmaceutical compositions and methods of treatment using previously uncharacterized individual isomers.

One of skill in the art would recognize that an individual isomer, substantially separated from its counterpart, would be as likely to have deleterious qualities making it unsuitable or less suitable for pharmaceutical use, when compared to the racemate and/or the counterpart isomer. Accordingly, the courts' statements as quoted above acknowledge unpredictability that supports the nonobviousness of the methods presently disclosed and claimed.

Applicants note that the technical literature has shown that it is unpredictable which isomer, if any, will be effective in a pharmaceutical formulation for treatment of a disorder. Based on other references, including Stone, *et al.* (*J. Med. Pharm. Chem. 5(4)*:665-90 (1962); reference already provided), there was no difference in activity between the racemate and isomers. In addition, in Suchocki, *et al.* (*J. Med. Pharm. Chem. 34*:1003-1010 (1999); reference already provided), both the (-) and (+) antipodes of exo-mecamylamine were found to have similar potency to the racemate for antagonism of nicotine-induced flociception. The Stone and Suchocki references indicate that the art lacks the motivation to prepare a pharmaceutical formulation of a highly purified (and much more expensive) mecamylamine isomer.

Applicants believe that the claimed methods of treatment using the exo-R-mecamylamine isomer are not obvious for at least the reason that the prior art taken as a whole teaches no difference in activity. Therefore, at the time of the present invention, no motivation was provided to undergo the considerable expense of isolating the exo-R isomer and putting the isomer into a pharmaceutical formulation for use in treating the recited disorders.

Accordingly, it is submitted that the Office Action does not set out a *prima facie* case for obviousness over USF, assuming solely for the sake of argument, that the international publication was properly cited as prior art. However, Applicants wish to reiterate that the international publication is not prior art for the pending claims because they were fully supported in the parent applications, at least back to the international filing date of the parent PCT application on December 16, 1999.

Again, regarding the Examiner's comments concerning the suggested use of the terms "isolated" or "optical purity," Applicants respectfully assert that the recited exo-R-mecamylamine is distinguished from racemate compositions by the recitation "substantially free of exo-S-mecamylamine," as defined in Applicants' specification.

For at least the foregoing reasons, USF fails to teach or suggest the claimed methods. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Conclusion

All alleged bases for rejection of Applicants' pending claims have been properly traversed in view of the foregoing remarks. Accordingly, the present application is in condition for immediate allowance, and early notice to that effect is earnestly solicited.

The Examiner is invited to contact Applicants' undersigned representative using the information provided below if she has any questions or comments regarding this Reply.

Respectfully submitted,

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